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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,734	06/25/2001	Bruce Joseph Roser	GJE-6089D1	2528

23557 7590 12/06/2002

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EXAMINER	
PRATS, FRANCISCO CHANDLER	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 12/06/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,734	ROSER, BRUCE JOSEPH	
	Examiner	Art Unit	
	Francisco C Prats	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed September 30, 2002, has been received and entered. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Claims 14-19 have been added.

Claims 1-19 are pending and are examined on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Roser (BioPharm 4(8):47-53 (September 1991)) (Roser I).

Roser clearly discloses that trehalose has been used as a preservative agent for Factor VIII in dried form. *See* p. 52. ("Trehalose, on the other hand, is extremely stable and confers on the product the same resistance to hostile environments enjoyed by cryptobiotic organisms. Similar data have been

obtained with a large range of biological molecules, including a panel of monoclonal antibodies against human blood groups and pharmaceutical proteins such as recombinant Factor VIII.") Roser I makes no mention of using albumin with the trehalose.

A holding of anticipation is clearly proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms he basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roser (BioPharm 4(8):47-53 (September 1991)) (Roser I) and Livesey et al (U.S. Pat. 5,364,756) in view of Roser (U.S. Pat. 4,891,319)(Roser II) and Lee et al (EP 0 314 095).

As discussed above, Roser I discloses the use of trehalose in preserving factor VIII in the absence of albumin. Moreover, Livesey discloses the drying of biological materials including Factor VIII (*see* claim 17) in cryoprotectant solutions

comprising trehalose in the absence of serum albumin (*see* claim 9), wherein the drying is performed at ice-forming temperatures. Although it is not clear that Roser I and Livesey disclose the exact amounts of trehalose and calcium ion claimed, note specifically that Livesey clearly discloses the suitability of using calcium-containing buffers in the cryoprotectant methods disclosed therein. Moreover, Lee et al clearly discloses the desirability of using the claimed amount of calcium chloride in buffers for use in lyophilizing factor VIII. Thus, applicant's selection of a concentration of calcium known to be useful in the preservation of factor VIII clearly would have been obvious at the time of applicant's invention. Note specifically Roser I's discussion regarding the requirement of buffers in which the biological molecule is active, at pages 48 and 49. Note further that Lee clearly discloses that Factor VIII is active at the claimed calcium concentration.

Regarding the claimed amount of trehalose, Roser II clearly discloses that the amount of trehalose to be used in preserving biological materials is routinely optimized, depending on the amount of protein present in the sample to be preserved. *See* col. 3, lines 21-31. Thus, determination of a specific amount of trehalose, including that claimed would have been a routine

matter of optimization on the part of the artisan of ordinary skill, and therefore clearly obvious under 35 U.S.C. § 103(a).

Lastly, regarding the reconstitution of the dried materials in saline or water, note specifically that at the time of applicant's invention it was well known that both of these vehicles was suitable for injection, the known method of administration of Factor VIII. A holding of obviousness is therefore required.

Claims 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat. 5,576,291) in view of Livesey et al (U.S. Pat. 5,364,756).

Curtis et al disclose the preparation of albumin-free Factor VIII, including recombinant Factor VIII as recited in new claims 25 and 28. *See* Example 1 at col. 6, line 37 through col. 7, line 62. Note specifically that the process performed by Curtis includes column chromatography which separates proteins from each other, and would therefore necessarily result in an albumin-free preparation. Curtis differs from the claims in that Curtis does not actually exemplify a single embodiment whereby the Factor VIII is freeze-dried in the presence of trehalose.

However, Curtis clearly discloses that the preparation can be stabilized by trehalose. *See* col. 4, lines 65-67. ("Examples of stabilizers include albumin … and trehalose.") Curtis further discloses that "[f]ollowing preparation and stabilization of the activated Factor VIII, the protein can be lyophilized and stored at reduced temperatures …." Col. 5, lines 4-6. Thus, the artisan of ordinary skill reading only the Curtis disclosure clearly would have been motivated to have lyophilized an albumin-free preparation of Factor VIII in trehalose.

Moreover, Livesey discloses that a number of biological materials, including Factor VIII (*see* claim 17, at col. 26, lines 11 and 12), can be preserved by freeze-drying (*see* claim 11, at col. 25, lines 55 and 56) in a solution containing 6% trehalose in the absence of albumin (*see* claim 9, at col. 25, lines 37-44). Thus, while Livesey differs from claim 7 in not disclosing a single embodiment having all of the claimed limitations, Livesey clearly provides motivation for placing an albumin-free preparation of Factor VIII, such as that produced by Curtis, into a trehalose-containing solution and freeze drying the solution. A holding of obviousness is therefore clearly required

It is noted that new claims 15 and 18 require the Factor VIII to be "native" Factor VIII. However, Livesey clearly provides motivation for lyophilizing "native" Factor VIII in trehalose without albumin by not only claiming a specific embodiment (claim 17) of lyophilizing Factor VIII, but also disclosing that trehalose, and not albumin, is one of a number of agents particularly suited to dry preservation of macromolecules such as proteins. See col. 9, lines 16 -32:

> For example, trehalose and polyhydroxyl carbohydrates bind to and stabilize macromolecules such as proteins and nucleic acids in a virus or vaccine sample when dried, thereby protecting the integrity of the sample. Various dry protectants can be used in the present invention: sucrose, raffinose, trehalose, zinc, proline (or other protein stabilizers), myristic acid (a known thermostabilizer of vaccines), spermine (a polyanionic compound) and combinations thereof.

Thus, the artisan of ordinary skill seeking to preserve the "native" Factor VIII encompassed by Livesey's claim 17, recognizing that Factor VIII is a protein, clearly would have looked to trehalose instead of albumin, based on Livesey's disclosure that trehalose is one of a number of agents particularly suited for protein protection in freeze-drying procedures, and albumin is not. Additional motivation for freeze-drying Factor VIII using trehalose in the absence of albumin would have been derived from the fact that the lone example of protein freeze-drying of Livesey, Example 5 at

columns 23 and 24, demonstrates that the integrity of a protein-containing viral vaccine is adequately protected by trehalose in buffer with no other preservative agents.

Double Patenting

Claims 14-19 of this application conflict with claims 7 and 24-28 of Application No. 08/875,796. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 14-19 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 7 and 24-28 of copending Application No. 08/875,796. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No 4,891,319 (Roser II), in view of Roser (BioPharm 4(8):47-53 (September 1991)) (Roser I) and Livesey et al (U.S. Pat. 5,364,756) and Lee et al (EP 0 314 095).

The claims of the '319 patent (Roser II) clearly recite methods wherein any and all proteins and biological macromolecules are protected against denaturation by drying with trehalose. Note specifically the suitability of the method for "enzyme serum" (claim 3 at col. 13), from denaturation. In view of Roser I's and Livesey's disclosure that Factor VIII can be readily preserved according to the methods claimed by the '319

patent, the instant claims are clearly obvious over the previously patented claims, to the extent they recite drying Factor VIII in the presence of trehalose, including at the claimed trehalose concentrations. Further still, the instant claims' recitation of specific amounts of calcium ion are clearly obvious over the '319 patent's claims, in view of Livesey and Lee's disclosure of the suitability of calcium in the trehalose/Factor VIII composition, and particularly in view of Roser I's disclosure of the requirement of buffer components in which the biological material is active.

In sum, the '319 claims' clear disclosure of the suitability of any and all biological materials, including proteins, combined with Roser I's clear disclosure of Factor VIII's amenability to the '319's claimed methods, clearly makes the instant claims obvious over the '319 patent. Moreover, the prior art's disclosure of the desirability of the presence and amounts of the claimed ingredients clearly demonstrates the obviousness of all the claims over applicant's previous '319 patent.

Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 24-28 of copending Application

No. 08/875,796, in view of Roser (BioPharm 4(8):47-53 (September 1991)) (Roser I) and Livesey et al (U.S. Pat. 5,364,756) and Lee et al (EP 0 314 095). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims' recitation of drying at a temperature of less than 10 degrees C clearly encompasses the freeze drying recited in claim 7 of '796 application. Moreover, the product resulting from the process recited in claim 7 of the '796 application clearly renders obvious the presently claimed products, particularly in view of the Roser, Livesey and Lee references, which suggest the use of salts in the lyophilization buffer. Further still, the use of the lyophilized factor VIII product in reconstituted form, as recited in instant claims 11-13, for injection clearly would have been obvious as injection was the known method of administering factor VIII.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

AS discussed immediately above, and in the previous office action, claims 1-13 of this application conflict with claims 7 and 24-28 of Application No. 08/875,796. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims

from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Response to Arguments

All of applicant's argument has been fully considered but is not persuasive of error. With respect to the issue of anticipation, Roser I clearly states that trehalose, by itself, is suitable for stabilizing Factor VIII. The reference clearly anticipates claims 1-3. While applicant points to a number of publications disclosing the addition of albumin to Factor VIII compositions, this does not demonstrate that Roser I's Factor VIII/trehalose preparations contain albumin. Exhibit 1 refers only to "licensed" products. Exhibit 2 simply points out that one may lyophilize Factor VIII in the presence of albumin, a fact already apparent from the record. Exhibits 1 and 4 are directly contradicted by Roser I, which clearly suggests that proteins such as Factor VIII may be preserved by drying in the presence of trehalose alone. Exhibit 3 simply discloses that one may stabilize Factor VIII with albumin, and does not address

the suitability of trehalose-containing formulations for this purpose.

Similarly, Exhibits A through G merely disclose that albumin was used to stabilize to Factor VIII. These references mention nothing about trehalose, and none of the references provide any direct evidence about whether Roser I's preparations inherently, or necessarily contained albumin.

In essence, applicant argues that the Factor VIII preparations described by Roser I inherently contain albumin. However, as discussed in the caselaw cited in applicant's argument, it is well established that inherency cannot be based on probability or likelihood, the exact means applicant is attempting to employ. Thus, contrary to applicant's argument, it is not a "bold proposition" to assert that the composition disclosed by the reference necessarily lacks albumin. Using the language of the statute, Roser I clearly "describes" a dried composition containing trehalose and Factor VIII in the absence of albumin. Because Roser I does not mention albumin, Roser I exactly "describes" a composition which does not contain "a stabilizing amount of albumin." In fact, from a logical standpoint it is clearly a much bolder proposition to assert that an ingredient is *necessarily present because the reference fails to mention it*. Using applicant's logic, one could assert

that any prior art composition must necessarily contain any undisclosed ingredient, based on a probability that said undisclosed ingredient would be present in the prior art composition. That is clearly not the state of the law. Applicant clearly bears the burden of demonstrating a difference between the claims and a prior art reference which, on its face, so plainly meets the statutory requirements of 35 U.S.C. § 102(b). A holding of anticipation over Roser I clearly remains required.

Regarding the issue of obviousness, note specifically that Dr. Mackenzie's declaration is directly contradicted by Curtis and Livesey, each of which suggests that proteins such as Factor VIII may be preserved by freeze-drying in the presence of trehalose alone.

Moreover, as discussed above, Livesey clearly provides motivation for lyophilizing "native" Factor VIII in trehalose without albumin by not only claiming a specific embodiment (claim 17) of lyophilizing Factor VIII, but also disclosing that trehalose, and not albumin, is one of a number of agents particularly suited to dry preservation of macromolecules such as proteins. See col. 9, lines 16 -32. Thus, the artisan of ordinary skill seeking to preserve the "native" Factor VIII encompassed by Livesey's claim 17, recognizing that Factor VIII

is a protein, clearly would have looked to trehalose instead of albumin, based on Livesey's disclosure that trehalose is one of a number of agents particularly suited for protein protection in freeze-drying procedures, and albumin is not. Additional motivation for freeze-drying Factor VIII using trehalose in the absence of albumin would have been derived from the fact that the lone example of protein freeze-drying of Livesey, Example 5 at columns 23 and 24, demonstrates that the integrity of a protein-containing viral vaccine is adequately protected by trehalose in buffer with no other preservative agents. Thus, Livesey does not suggest that albumin is "necessary" for stabilization of Factor VIII. Moreover, when taken in light of Livesey, it is clear that the secondary references do not teach away from the use of trehalose to stabilize Factor VIII in the absence of albumin, as taught by Livesey.

Regarding the Curtis reference, the differences between native and activated Factor VIII are noted. However, as discussed at length above, the fact that Curtis stabilizes activated factor VIII does not demonstrate non-obviousness, particularly when most of claims 14-19 encompass activated Factor VIII, and when Livesey so clearly suggests that trehalose in the absence of albumin is particularly suited to the preservation of proteins such as Factor VIII. Lastly, although

applicant does not address the issue directly, it is confusing why applicant continues to prosecute identical and nearly identical claims in copending application 08/875,796. This procedure appears to clearly be improper. See MPEP § 822.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 703-308-3665. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Francisco C Prats
Primary Examiner
Art Unit 1651

FCP
December 5, 2002